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BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte JEFFREY D. WUITSCHICK and SHIHAI HUANG

Appeal 2017-009266
Application 14/015,251[1]
Technology Center 1600

Before FRANCISCO C. PRATS, ELIZABETH A. LAVIER, and RYAN H. FLAX, *Administrative Patent Judges*.

LAVIER, *Administrative Patent Judge*.

DECISION ON APPEAL

Pursuant to 35 U.S.C. § 134(a), Appellants seek review of the Examiner's rejections of claims 29, 32, 35–41, 44, 51–55, 57–60, and 68–70. We have jurisdiction under 35 U.S.C. § 6(b). For the reasons set forth below, we AFFIRM.

BACKGROUND

The Specification relates to molecular assays for the detection and analysis of PRAME (Preferentially Expressed Antigen in Melanoma), and the use thereof in cancer diagnosis and prognosis. *See* Spec. 1:8–26.

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[1] Appellants state the real party in interest is Abbott Molecular Inc. Appeal Br. 3.

Claim 29, the only independent claim on appeal, recites:

> 29. A method of detecting the presence or amount of PRAME (Preferentially Expressed Antigen in Melanoma) mRNA in a sample comprising:
>
> a) contacting a sample suspected of containing PRAME mRNA with a first primer and a second primer under conditions such that a first cDNA amplification product is generated, wherein said first primer hybridizes to Exon 3 of said PRAME mRNA, and wherein said second primer hybridizes to Exon 4 of said PRAME mRNA and wherein-said first and second primers are a primer pair selected from the group consisting of: SEQ ID NOs: 3 and 7; SEQ ID NOs: 4 and 8; SEQ ID NOs: 5 and 9; and SEQ ID NOs: 6 and 10 *wherein said contacting does not generate detectable amplicons from genomic PRAME*;
>
> b) providing at least one probe that is complementary to said first cDNA amplification product wherein said probe comprises a label; and
>
> c) detecting said first cDNA amplification product, thereby determining the presence and/or amount of said PRAME in said sample.

Appeal Br. 28 (Claims Appendix) (emphasis and some formatting added).

REJECTIONS MAINTAINED ON APPEAL

1. Claims 29, 32, 35, 36, 38, 44, 54, 55, 57, 58, 68, 69, and 70 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Pollack[2]

[2] Pollack et al., *NYESO-1/LAGE-1s and PRAME Are Targets for Antigen Specific T Cells in Chondrosarcoma following Treatment with 5-Aza-2-Deoxycitabine*, 7 PLoS ONE 1 (2012) (e32165).

and Mansfield,[3] as further evidenced by GenBank.[4] Ans. 2; Final Action 4.

2. Claims 37 and 39–41 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Pollack, Mansfield, and Sorge,[5] as further evidenced by GenBank. Ans. 16; Final Action 9–10.

3. Claims 51–53 and 59 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Pollack, Mansfield, and Colbeigh,[6] as further evidenced by GenBank. Ans. 19; Final Action 11.

4. Claim 60 stands rejected under 35 U.S.C. § 103(a) as unpatentable over Pollack, Mansfield, Colbeigh, Chen,[7] and Palma,[8] as further evidenced by GenBank. Ans. 21–22; Final Action 12–13.

DISCUSSION

The Examiner's thorough findings and analysis of the § 103 rejections are set forth in pages 4–14 of the Final Action and are further explained in pages 2–24 of the Answer. Having considered Appellants' arguments, we discern no reversible error in the Examiner's conclusions in regard to any of

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[3] Mansfield et al., WO 2005/070086 A2, published Aug. 4, 2005.
[4] GenBank, *Homo sapiens preferentially expressed antigen in melanoma (PRAME), transcript variant 1, mRNA*, Accession No. NM_006115 GI 4659365 (2004).
[5] Sorge, US 2007/0015180 A1, published Jan. 18, 2007.
[6] Colbeigh et al., *Tumor Gene Expression and Prognosis in Breast Cancer Patients with 10 or More Positive Lymph Nodes*, 11 CLIN. CANCER RES. 8623 (2005).
[7] Chen et al., US 2006/0269967 A1, published Nov. 30, 2006.
[8] Palma et al., US 7,374,927 B2, issued May 20, 2008.

Rejections 1–4, *supra*, for the reasons already of record and as further explained below.

A. Rejection 1

Pollack notes that PRAME is a promising target for T cell therapy in the treatment of chondrosarcoma, and reports that PRAME expression can be induced following treatment with 5-Aza-dC.[9] Pollack Abstract. The Examiner makes the following findings in regard to exemplary claim 29:

> Pollack teaches a method of detecting the amount of PRAME mRNA in chondrosarcoma samples and melanoma cell lines. Pollack teaches contacting the samples with a primer pair and performing quantitative real time PCR (with SYBR green as the reporter) to detect the amount of PRAME mRNA in the samples (page 2, col 2). Pollack discloses PRAME **specific** primers (see Table 1). As evidenced by GenBank the first primer 5'-GCTTCAAAATGGAACGAAGG-3' is 100% identical to nucleotides 242–261 of the GenBank sequence and hybridizes to exon 3 (nucleotides 152–270). The second primer 5'-TGCCAGCTCCACAAGTGTC-3' is 100% complementary to nucleotides 339–321 of the GenBank sequence and hybridizes to exon 4 (nucleotides 271–573). Thus Pollack teaches a method comprising contacting a sample suspected of containing PRAME mRNA with a first primer and a second primer under conditions such that a first cDNA amplification product is generated, wherein the first primer hybridizes to Exon 3 and the second primer hybridizes to Exon 4; and detecting the first cDNA amplification product thereby determining the presence and/or amount of PRAME mRNA in the sample.

Final Action 4–5. The similarity of the claimed primers and those of the prior art can be seen readily in the GenBank sequence as annotated by the

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[9] 5-Aza-2-Deoxycitabine.

Examiner, which illustrates the relationships between Pollack's primers (underlined) and the claimed primers (bolded), along with the exon 3/exon 4 junction (starred):

181 ggcaacaagt gactgagacc tagaaatcca agcgttggag gtcctgaggc cag**cctaagt**
241 **cgcttcaaaa tggaacg**aaa gcgtttgtgg*ggttccattc agagc**cgata catcagcatg**
301 **agtgtgtgga** caaagcccacg gagacttgtg gagctggcag ggcagagcct gctgaaggat
361 gaggccctgg ccattgccgc cctggagttg ctgcccaggg agctcttccc gccactctte
421 atggcagcct ttgacgggag acacagccag accctgaagg caatggtgca ggcctggccc
481 ttcacctgcc tccctctggg agtgctgatg aagggacaac atcttcacct ggagacctte
541 aaagctgtgc ttgatggact tgatgtgctc cttgcccagg aggttcgccc caggaggtgg

Id. at 5. The annotated sequence above illustrates the relationships between the prior art and claimed primers.

The Examiner acknowledges that Pollack's PRAME primers are not the same as SEQ ID NOs: 3 and 7 of claim 29,[10] and Pollack does not teach that its primers do not generate detectable amplicons from genomic PRAME (claim 29) or from known PRAME-like genes or mRNAs in the human genome (claim 70). *Id.* at 5. But the Examiner finds it would have been a matter of routine experimentation, with "more than a reasonable expectation of success," for the ordinarily skilled artisan to design primers which, like those of Pollack, would amplify across the PRAME exon 3/4 junction. *Id.* at 6. The motivation for doing so would have been "to obtain additional primers that could be used to measure the level of PRAME mRNA by amplifying across the exon 3/4 junction of PRAME and identify primers

[10] The Examiner notes that "Appellants elected the primer pair of SEQ ID NOs: 3 and 7 for examination and that the claims have only been examined to the extent that they read on the elected primer pair (SEQ ID NOs: 3 and 7). The additionally recited primer pairs have been withdrawn from consideration as being directed to nonelected subject matter." Ans. 3.

with improved properties." *Id.* Further, the Examiner finds that "it is a property of the claimed primers that they do not generate detectable amplicons from genomic PRAME and that they do not generate detectable amplicons from known PRAME-like genes or mRNAs in the human genome." *Id.*

As Pollack does not teach using a labeled probe complimentary to the amplification product as required by claim 29, the Examiner turns to Mansfield. *See* Final Action 7–9. Mansfield generally describes methods for determining whether a subject has a graft-tolerant phenotype, including by measuring gene expression through assaying a nucleic acid transcript of the gene. *See* Mansfield 2:21–3:1. To this end, Mansfield provides a protocol for TaqMan-based quantitative RT-PCR and sequences for various labeled probes, including a PRAME probe. *See id.* 24:26–25:12. The Examiner finds:

> Mansfield teaches a TaqMan probe 5'FAM-CGTTTGTGGGGTTCCATTCAGAGCC-NFQ3' for detecting PRAME (see pages 24–25). The part that is not underlined hybridizes to exon 3 and the part underlined hybridizes to exon 4. The probe of Mansfield shares 85% sequence identity with SEQ ID NO: 11.[11] The probe of Mansfield is 25 base pairs long and comprises nucleotides 5-26 of SEQ ID NO: 11. Because one uses multiple copies of the same probe in TaqMan PCR, one copy of the probe can be interpreted as a first primer that hybridizes to Exon 3 of PRAME and another copy of the probe can be interpreted as a second primer that hybridizes to

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[11] SEQ ID NO: 11 is among the sequences listed in claim 55, which ultimately depends from claim 29 and recites: "The method of claim 54, wherein said probe comprises at least 70% sequence identity with a sequence selected from the group consisting of SEQ ID NOs: 11-16." Appeal Br. 30 (Claims Appendix).

> exon 4 of PRMAE [*sic*]. It is noted for the record that the probe is labeled at it[s] 5' end with FAM with is a fluorescent dye and labeled at its 3' end with NFQ which is a non-fluorescent quencher.

Final Action 7–8. As with the primers discussed above, the sequence data as annotated by the Examiner are useful in visualizing the similarity of Mansfield's probe (underlined) and the claimed probe SEQ ID NO: 11 (bolded), in relationship to the PRAME exon 3/4 boundary (starred):

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181 ggcaacaagt gactgagacc tagaaatcca agcgttggag gtcctgaggc cagcctaagt
241 cgcttcaaaa tggaacgaag gcgatttgtgg*gattccattc agaaccgata catcagcatg
301 agtgtgtgga caagcccacg gagacttgtg gagctggcag ggcagagcct gctgaaggat
361 gaggccctgg ccattgccgc cctggagttg ctgcccaggg agctcttccc gccactcttc
421 atggcagcct ttgacgggag acacagccag accctgaagg caatggtgca ggccctggcc
481 ttcacctgcc tccctctggg agtgctgatg aagggacaac atcttcacct ggagaccttc
541 aaagctgtgc ttgatggact tgatgtgctc cttgcccagg aggttcgccc caggaggtgg
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Final Action 8. The annotated sequence above illustrates the relationships between the prior art and claimed probes.

Accordingly, the Examiner concludes:

> As demonstrated by Mansfield TaqMan-based quantitative RT-PCR was routinely used in the art at the time of the invention to detect the level of PRAME mRNA in a sample. Thus the substitution of one assay that detects gene expression (the syber green assay of Pollack) for another assay that also detects gene expression (the TaqMan PCR assay of Mansfield) would have yielded predictable results to one of ordinary skill in the art at the time of the invention . . . . A skilled artisan would be motivated to have designed and tested new probes to obtain additional probes that could be used to measure the level of PRAME mRNA by detecting the exon 3/4 junction of PRAME and identify probes with improved properties.

Id. at 8–9; *see also* Ans. 14–15.

Appellants' arguments to the contrary (*see generally* Appeal Br. 17–24; *see also* Reply Br. 3–11) are not persuasive. Appellants first take issue with the Examiner's determination that the claimed primers and probes are "equivalent" to the prior art. Appeal Br. 19–20; *see also* Reply Br. 5–6. But the Examiner provides an extensive, well-reasoned, and persuasive analysis in the Answer:

> The primer pair of the present invention was considered by the Examiner to be equivalent to the primer pair of Pollack because both primer pairs are used to amplify PRAME mRNA, both primer pairs comprise a first primer that hybridizes to exon 3 of PRAME and a second primer that hybridizes to exon 4 of PRAME, both primer pairs do not generate detectable amplicons from genomic PRAME, both primer pairs are considered to be specific for PRAME, and the first primer of Pollack is substantially identical to SEQ ID NO: 3. Thus it is maintained that the primer pair of Pollack is equivalent to the claimed primer pair for at least these reasons.

Ans. 6.[12]

Relatedly, Appellants maintain that "[t]here are untold millions of possible primer pairs that could be tested," and thus selecting the claimed primers and probes would not have been obvious to try, nor the result of routine experimentation or optimization. Appeal Br. 20. Appellants overstate the case; primer selection is constrained by various considerations,

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[12] Appellants characterize the design of RT-PCR primers as "laborious and error prone," and thus not a matter of routine experimentation (Reply Br. 6), quoting a supporting reference, Cui, cited in Pollack and discussed by the Examiner in the Answer (and earlier in the record) (*see* Ans. 4 (citing Cui et al., *qPrimerDepot: a primer database for quantitative real time PCR*, 35 NUCLEIC ACIDS RES. D805 (2007)). But this quotation comes from Cui's introduction, and is not a description of Cui's own methodology. It is the latter on which the Examiner relies. *See* Ans. 4.

both as a general matter and in regard to the design of primers to bridge the exon 3/exon 4 boundary of PRAME, and similarly in regard to probe design:

> Designing probes which are equivalent to those taught in the art is considered routine experimentation particularly since the nucleic acid sequence of the PRAME mRNA was known in the art as demonstrated by GenBank. The prior art is replete with guidance and information necessary to permit the ordinary artisan to design probes for measuring the level of PRAME mRNA by detecting the exon 3/4 junction of PRAME. The ordinary artisan would have had more than a reasonable expectation of success of making probes for measuring the level of PRAME mRNA by detecting the exon 3/4 junction of PRAME. Thus at the time of the invention, the skill in the art, the computer software available (PrimerDepot, BLAST, etc.), and the guidance provided by the prior art would have made selecting the probes recited in the claimed method obvious. A skilled artisan would be motivated to have designed and tested new probes to obtain additional probes that could be used to measure the level of PRAME mRNA by detecting the exon 3/4 junction of PRAME and identify probes with improved properties. Further the skilled artisan would have found it obvious to try the probes recited in the claimed method because the artisan would have had a finite number of identified, predictable sequence options for the probes, and the artisan would have had good reason to pursue these known options, which were within the artisans technical grasp.

Final Action 9; *see also id.* at 6, Ans. 7–8.

Indeed, another panel of the Board rejected a similar argument alleging the non-obviousness of selecting particular primers from known sequences:

> Thus, if [*In re Kubin*, 561 F.3d 1351, 1360 (Fed. Cir. 2009)] finds that cloning an unknown gene sequence had a "reasonable expectation of success," we conclude that it is more than reasonable to find that selection of particular real-time primer sequences from a known sequence using commercially available software "would have had a resoundingly 'reasonable

> expectation of success' in deriving the claimed invention in light of the teachings of the prior art." *Kubin*, 561 F.3d at 1360.

Ex parte Kostrikis, Appeal No. 2010-001111, 2010 WL 2694707, at *7 (July 2, 2010).[13] We concur with our colleagues that selecting particular primers from known sequence data (and in light of known equivalent primers) cannot confer patentability to otherwise obvious claims, at least not in the absence of persuasive contrary evidence. Even though a great many primer or probe sequences may be theoretically possible, selecting particular primers or probes from a known sequence, especially those so similar to prior art primers/probes,[14] is a matter of routine experimentation nonetheless, on the current record. As the Examiner puts it: "[t]he Appellants have not established that the primers/probes are non-obvious with persuasive evidence by merely asserting that the probability of picking the claimed primer pair and probe would have been unlikely." Ans. 7–8.

Appellants' related assertion that the Examiner bears the burden to provide evidence that "Pollack's primers do not generate detectable amplicons form known PRAME-like genes or mRNAs" (Reply Br. 5 (discussing claim 70)) is likewise unpersuasive. The rejection relies on the Examiner's inference that because Pollack's primers are so close in

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[13] The art cited to support the obviousness rejection appealed in *Kostrikis* included a large number of functional primer pairs (*see* 2010 WL 2694707, at *4), whereas here, Pollack teaches a single pair of PRAME primers across the exon 3/4 boundary (*see* Pollack Table 1). Nonetheless, as discussed above, the Examiner's finding that Pollack's primers are equivalent to the claimed primers is well-supported.

[14] As the Examiner emphasizes: "the first primer of Pollack is substantially identical to SEQ ID NO: 3 and [] the probe of Mansfield overlaps the probe of SEQ ID NO: 11." Ans. 8.

sequence to the claimed primers, Pollack's primers would share functional characteristics with the claimed primers, i.e., non-generation of unwanted amplicons (be they from genomic PRAME or PRAME-like genes or mRNAs). *See* Ans. 5 ("Considering that the first primer of Pollack is substantially identical to SEQ ID NO: 3, there was a reasonable expectation in the art that the first primer of Pollack will also have the same property of SEQ ID NO: 3 of not generating detectable amplicons from known PRAME-like genes or mRNAs."); *see also* Final Action 5–6. This inference is reasonable, and shifts the burden to Appellants to produce evidence to the contrary:

> [W]here the Patent Office has reason to believe that a functional limitation asserted to be critical for establishing novelty in the claimed subject matter may, in fact, be an inherent characteristic of the prior art, it possesses the authority to require the applicant to prove that the subject matter shown to be in the prior art does not possess the characteristic relied on. . . . Whether the rejection is based on 'inherency' under 35 U.S.C. § 102, on 'prima facie obviousness' under 35 U.S.C. § 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products.

In re Best, 562 F.2d 1252, 1254-55 (CCPA 1977) (footnote omitted) (citations omitted). Appellants have not done so, and thus the Examiner's inference stands. Accordingly, Appellants' further assertion that the Examiner cannot rely on the inherent properties of the claimed primers to satisfy the claim limitations of not generating detectable amplicons from genomic PRAME (claim 29) or from known PRAME-like genes or mRNAs in the human genome (claim 70), because "[t]here is no guidance in the cited

art that seeks this goal, or that accomplishes it" (Appeal Br. 20; *see also* Reply Br. 3–5) is equally unpersuasive.

Appellants next argue that Pollack's methods lack utility and that Pollack provides a different solution to a different problem than the claimed invention. *See* Appeal Br. 21–24. We are not persuaded. As the Examiner explains (describing Pollack):

> PRAME was expressed in the untreated cell lines at a relatively low level. However PRAME expression was *increased significantly* following 5-Aza-dC treatment. The SAME methodology and primers were used to measure PRAME expression before and after treatment with 5-Aza-dC. The fact PRAME expression levels were relatively low in the chondrosarcoma cell lines prior to treatment with 5-Aza-dC is due to the fact that this is a property of the sample-it is NOT attributable to the methodology or primers that were used by Pollack. If it had been attributable to the methodology or primers that were used by Pollack then Pollack would not have been able to detect the significant increase in PRAME expression that was observed after the treatment with 5-Aza-dC (see Fig 1B). Further Pollack would have wanted to avoid generating amplicons from PRAME-like genes or mRNAs because Pollack was interested in determining whether treatment with 5-Aza-dC could specifically induce PRAME expression.

Ans. 10–11. We also note that to the extent Appellants' arguments critique Pollack as being insufficient to detect increased PRAME expression "in cells from patient samples" (Appeal Br. 24), claim 29 does not specify that the sample must contain intact patient cells.

Further as to Mansfield, Appellants assert the rejection engages in too much picking and choosing, and offers no rationale for combining such diverse references. *See* Appeal Br. 24. According to Appellants, "[t]he Office provides no evidence that Mansfield's probe configured for

determining a graft tolerant phenotype in the circulating blood of a subject provides a working method in combination with Pollack's methods and reagents for determining targets for antigen specific T-cells in chondrosarcoma." *Id.* Appellants emphasize that "Mansfield's method of detecting PRAME expression uses a labeled target hybridized to a cDNA microarray, not a labeled probe." Reply Br. 7 (citing Mansfield 11:10–18). These arguments are not persuasive. First, they largely focus on Mansfield individually rather than the combination of references. *See In re Keller*, 642 F.2d 413, 426 (CCPA 1981) ("But one cannot show non-obviousness by attacking references individually where, as here, the rejections are based on combinations of references."). Second, as the Examiner explains, Mansfield provides data showing differential PRAME expression, and provides a method for detecting it:

> Figure 1 of Mansfield provides Table 1, which lists 200 representative genes whose expression differs in operationally tolerant (OT) patients relative to those with chronic graft injury (see page 5 lines 26-27 and Fig 1). PRAME is listed in Table 1 as having a 2.80 fold difference in expression between OT patients and those with chronic graft injury. Based on the PRAME data presented in the disclosure of Mansfield the skilled artisan would have concluded that the methodology and primers/probe of Mansfield did in fact work to detect PRAME expression.

Ans. 14. Further, Pollack and Mansfield are analogous art because both teach detecting PRAME mRNA in a sample by different methods, and thus it would have been obvious to substitute "one assay that detects gene expression (the syber green assay of Pollack) for another assay that also detects gene expression (the TaqMan PCR assay of Mansfield)" (Final Action 8; *see also* Ans. 15).

Having considered Appellants' arguments for the patentability of claims 29 and 70, we are not persuaded of any reversible error by the Examiner. We thus affirm the rejection of claims 29 and 70 under § 103(a). Claims 32, 35, 36, 38, 44, 54, 55, 57, 58, 68, and 69 are not argued separately, and fall with claims 29 and 70. *See* 37 C.F.R. § 41.37(c)(1)(iv).

B. Rejection 2

Appellants' arguments specific to these claims[15] begin by reciting what Sorge does not teach (*see* Appeal Br. 25), i.e., anything PRAME-specific, but the Examiner does not rely on Sorge for any such teachings, and so this argument unpersuasively argues the references individually instead of in combination. *See Keller*, 642 F.2d at 426.

Appellants then argue that the ordinarily skilled artisan would have had no reason to combine Sorge with the other references, and that "[t]he Office provides no evidence that Sorge's oligonucleotide pair 'complex' could be combined with Pollack, Mansfield and GenBank with a reasonable expectation of success at arriving at the methods of the present claims, or a working method of any kind." Appeal Br. 25; *see also* Reply Br. 12. This argument is likewise not persuasive, especially given the narrow purposes for which the Examiner employs Sorge:

> In the rejection, Sorge is only being relied upon to teach probes that are labeled with Cy5 or Quasar as required by claim 37, probes that comprise the quencher BHQ or BHQ2 as required by claim 39, and probes that have binding enhancers such as minor groove binders as required by claims 40 and 41. It is reiterated for the record that Pollack teaches detecting PRAME

[15] Appellants argue the claims subject to Rejection 2 as a group. *See* Appeal Br. 24–25.

> mRNA in a sample using a SYBR Green based quantitative real time PCR assay and that Mansfield teaches detecting PRAME mRNA in a sample using a TaqMan based quantitative real time PCR assay. The TaqMan based method of Mansfield uses a probe that is labeled at its 5' end with FAM which is a fluorescent dye and labeled at its 3' end with NFQ which is a nonfluorescent quencher to detect amplification. The skilled artisan would have been motivated to look at the relevant prior art of Sorge because this reference discloses numerous fluorophores and quenchers that are known in the art and can be used to detectably label oligonucleotide probes (see paras 0058-0063).

Ans. 17; *see also* Final Action 9–11.

Accordingly, we affirm the rejection of claims 37 and 39–41.

C. Rejection 3

As with Rejection 2, Appellants begin their separate arguments regarding Rejection 3[16] with a recitation of what Cobleigh does not teach, and continue by arguing that there would have been no reasonable expectation of success in combining Cobleigh with the other references. *See* Appeal Br. 25–26; *see also* Reply Br. 13. Again, these arguments are not persuasive to the extent they argue Cobleigh individually. *See Keller*, 642 F.2d at 426. As to the combination, we are not persuaded; again, the additional reference is only employed for narrow purposes and the Examiner offers a thorough rationale:

> Cobleigh is only being relied upon to teach detecting PRAME in a sample that is a formalin fixed and/or paraffin embedded sample as required by claim 51, detecting PRAME in a tumor sample as required by claim 52, detecting PRAME in a breast

[16] Appellants argue the claims subject to Rejection 3 as a group. *See* Appeal Br. 25–26.

> cancer sample as required by claim 53, and using beta-actin as a housekeeping mRNA as required by claim 59. It is reiterated for the record that Pollack teaches detecting PRAME mRNA in a sample using a SYBR Green based quantitative real time PCR assay and that Mansfield teaches detecting PRAME mRNA in a sample using a TaqMan based quantitative real time PCR assay. The skilled artisan would have been motivated to look at the relevant prior art of Cobleigh because this reference also teaches detecting PRAME mRNA in a sample using a TaqMan based quantitative real time PCR assay (see page 8624).

Ans. 19–20; *see also* Final Action 11–12.

Accordingly, we affirm the rejection of claims 51–53 and 59.

D. Rejection 4

Appellants' arguments specific to claim 60 begin by reciting what Chen and Palma do not teach. *See* Appeal Br. 25–26. These arguments are not persuasive because the Examiner does not rely on Chen or Palma for such teachings. *See Keller*, 642 F.2d at 426. Appellants further argue that "the Office provides no evidence that the skilled artisan interested in the primer pairs of the present claims would be motivated to combine Chen's primer sequence with Palma's probe sequence, or do so with a reasonable expectation of success in arriving at the claimed primer pairs." Appeal Br. 27 (emphases omitted); *see also* Reply Br. 14. We are not persuaded. As the Examiner explains, Chen and Palma are only relied upon for teaching specific primers for amplifying beta-actin mRNA as required by claim 60. *See* Ans. 22–23; *see also* Final Action 12–14. As with the design of the PRAME primers and probes discussed above with regard to Rejection 1, the Examiner is on similarly solid footing in concluding that "[b]ased on the teachings in the prior art the ordinary artisan would have had more than a

reasonable expectation of success of making primers for amplifying beta actin." Final Action 14.

Accordingly, we affirm the rejection of claim 60.

CONCLUSION

The Examiner's rejections of claims 29, 32, 35–41, 44, 51–55, 57–60, and 68–70 under 35 U.S.C. § 103(a) are each affirmed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv).

AFFIRMED